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Management of nonmetastatic muscle invasive bladder cancer in the elderly

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Summary A substantial increase in the number of elderly patients with muscle invasive bladder cancer (MIBC) is expected in upcoming years due to demographic changes and the peak incidence of bladder cancer in the 8th decade of life. The management of these patients is mainly driven by chronological age, comorbidities, tumor characteristics (unifocality, multifocality, concomitant carcinoma in situ, depth of invasion) and the presence of tumor-related symptoms (hematuria, pain, bladder dysfunction). A potential algorithm for the treatment of elderly patients with MIBC is presented. Ideally these patients are managed by a multidisciplinary team that includes an in-depth geriatric assessment and in centers experienced with MIBC to avoid any delay for—potentially—curative treatment.

Keywords Bladder tumour · Treatment · Cystectomy · Urinary diversion

Introduction

Bladder cancer is the most common malignancy of the urinary system and the 9th most common malignancy worldwide with 1638 new cases and 586 deaths in Austria 2016 [1]. Age is an independent risk factor for bladder cancer, thus, making it primarily a disease of the elderly, commonly occurring beyond the 70th year of life [2]. Data from the California Cancer Registry revealed a peak incidence of bladder cancer in the 85- to 95-year-old age group [2].

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Due to demographic changes the fastest growing population-segment is the age group of ≥85 years. Therefore, a substantial increase of elderly patients with bladder cancer can be expected. At diagnosis 20–25% of all patients harbor muscle invasive bladder cancer (MIBC) that—if left untreated—is a lethal disease with a 6-month cancer-specific mortality rate of 41% and a 5-year overall mortality rate of 95% [3].

The aim of this manuscript is to provide a short overview on some aspects of the management of elderly patients with nonmetastatic MIBC.

Radical cystectomy in the elderly

Open radical cystectomy (RC) with pelvic lymphadenectomy and urinary diversion is the surgical gold standard for MIBC. The median age at RC is around 65 years and approximately 25% of procedures are performed in patients older than 70 years. Despite relevant progress in surgical and anesthesiologic techniques, RC remains a complex procedure with a substantial morbidity and perioperative mortality [4].

There is a shift towards more advanced tumor stages at RC in elderly patients. Some authors propose that elderly patients with MIBC are not informed on potentially curative treatment options or that referral is delayed, leading to a worsened disease stage. Koppie et al. have shown that patients with a higher age adjusted Charlson comorbidity index (ACCI) had a longer interval from diagnosis of MIBC to curative treatment [5].

A few studies have specifically addressed the role of RC in the elderly. A retrospective, multicenter study on RC in patients >75 years included 256 patients with a mean age of 79.6 years [4]. Patients were followed for 3 months. In all, 41.4% of patients had an uneventful postoperative course (Clavien grade 0) and 26.6% developed severe complications (Clavien grade III–V). In

a multivariable regression analysis, a higher Charlson comorbidity index and higher body mass index were predictors for the development of complications [4]. Froehner et al. reviewed the complication rate of RC in the elderly [6]. In all series the early (90-day) complication rate (albeit using various definitions) ranged between 25 and 50% and in most series it was correlated with chronological age [6]. Reasons for the higher complication rate in the elderly are comorbidities, compromised physiological reserve and the reduced ability to respond to stressors.

In the above mentioned retrospective study, the 90-day mortality rate following RC was 9% which fits well with numbers in the literature [4]. There is a close correlation between early postoperative mortality and chronological age. For patients older than 80 years the odds ratios for the 90-day mortality rise 2.4–7.9 as compared to those younger than 70 years [7]. Comploj et al. reported in a multicenter study on the perioperative mortality of 251 patients older than 75 years [8]: the 30-day and 90-day mortality rates in the 75- to 84-year-old cohort were 4.5 and 13.5%, in the 85+ plus cohort the respective figures rose to 6.5 and 32.3% (!) [8].

The overall survival following RC in elderly patients is limited due to the aggressive nature of MIBC and comorbidities with advanced age. In a large series with 12,722 patients, the 1-year overall survival in the 70- to 79-year-old cohort was 76%, at 2 years 60% and at 5 years 42%; the respective values for the 80+ cohort were 64%, 46% and 23% [9].

Urinary diversion in the elderly

Old patients tolerate RC (particularly if performed extraperitoneally) well. The major source of postoperative complications of RC irrespective of age is urinary diversion with the use of bowel, which may result in morbidity, surgical reinterventions, prolonged hospital stay and high mortality [10]. One strategy to reduce risk and morbidity of RC in patients with advanced age is therefore to avoid the use of bowel by performing an ureterocutaneostomy (UC). In the middle of the last century, UC had been largely substituted by other forms of urinary diversion (ileum conduit, more recently orthotopic bladder substitute) mainly because of stoma-related complications. Modern stoma care, the advent of double J-catheters and most—importantly—the ever-increasing number of elderly frail patients requiring RC resulted in a renewed interest in this form of urinary diversion.

In the above-mentioned multicenter study of patients ≥75 years of age who underwent RC, 20% of patients received this form of urinary diversion [10]. As expected, patients who received an UC had a lower medical (23% vs 39%) and surgical (4% vs 38%) complication rate as compared to those with an ileal conduit [10]. In one of the most recognized, high-volume centers for surgical treatment of bladder cancer in Europe, 13% of patients aged 70–79 years and 48% of those older than 80 years who underwent RC received an UC as urinary diversion [11].

Bladder sparing approaches

The major attractive aspect of bladder sparing is to avoid risks and complications of RC/urinary diversion and to keep the genuine bladder. The two bladder sparing approaches are transurethral resection (TUR) monotherapy and trimodal therapy (radical TUR followed by radiochemotherapy). Not all MIBC must be managed by RC or trimodal therapy. Studies have shown that highly selected patients with isolated MIBC can be effectively treated by radical TUR monotherapy provided that there is a pT0 in a secondary section and no concomitant carcinoma in situ [12, 13]. In these series, overall and cancer-specific survival were comparable to RC cohorts [12, 13]. The standard bladder sparing approach comprises radical TUR followed by combined radio/chemotherapy. The majority of elderly/geriatric patients with MIBC have a compromised kidney function thus hindering chemotherapy; hence the majority of data regarding bladder sparing therapy in elderly/geriatric patients are based on TUR-bladder/radiotherapy [14]. Population-based and nonrandomized comparative trials (all associated with significant biases) revealed a similar survival following bladder sparing and RC [14]. A retrospective comparison between RC and bladder sparing approaches in geriatric patients (>80 years) also observed no survival difference between the two treatment strategies [15]. The presence of severe recurrent macrohematuria, upper urinary tract dilatation with compromised kidney function or significantly reduced bladder capacity usually prohibits an organ preserving strategy. Partial cystectomy is rarely indicated in muscle invasive urothelial bladder cancer yet might play a role in, for example, solitary muscle invasive squamous cell or urachal cancer.

Geriatric assessment

Current guidelines recommend that pre-RC risk assessment should take into account age, performance status, and comorbidity [16]. Conventional comorbidity indices perform inconsistently in accurate assessment of the risk of perioperative complications, prolonged rehabilitation, and long-term oncologic outcomes [16, 17]. Novel metrics including standardized assessments of dependency, comorbidity severity, sarcopenia, malnutrition, physical and cognitive frailty, and comprehensive geriatric assessments may offer more precise estimates of physiologic age and relative vulnerability to adverse outcomes following RC [16]. The use of standardized multidimensional instruments should be encouraged for patients undergoing consideration for RC to identify potentially modifiable risk factors that can be targeted with pre-

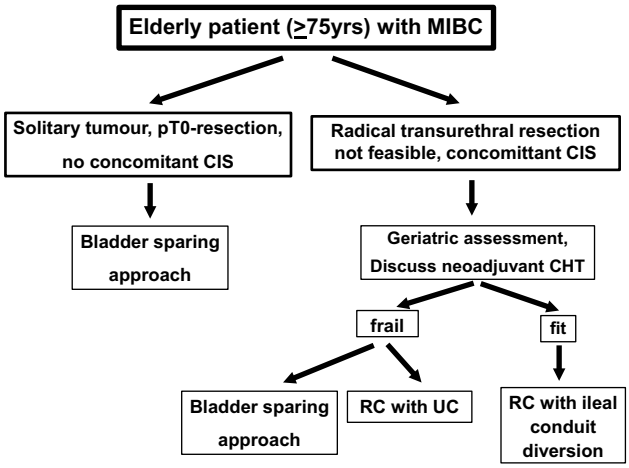

Fig. 1 Proposed algorithm for the management of elderly patients (≥75 years) with nonmetastatic muscle invasive bladder cancer. *CHT* chemotherapy, *MIBC* muscle invasive bladder cancer, *CIS* carcinoma in situ, *RC* radical cystectomy, *UC* ureterocutaneostomy

habilitation interventions [16, 17]. Future work is needed to validate the performance of these metrics prospectively with respect to predicting perioperative complications and oncologic outcomes and to define and assess the effectiveness of specific prehabilitation interventions to optimize patients before surgery [16, 17].

Palliative indication for radical cystectomy

A difficult clinical scenario is that of an elderly, frail patient with invasive bladder cancer complicated by recurrent macrohematuria requiring, for example, repeat endoscopic coagulation and blood transfusions, with severe bladder pain, urinary incontinence and/or upper urinary tract dilatation with renal failure. It is beyond the scope of this manuscript to present the various treatment options in these clinical scenarios (e.g., repeat TUR, embolization of the internal iliac artery, intravesical formaldehyde instillation). Some of these patients ultimately require palliative RC.

Role of neoadjuvant chemotherapy

Neoadjuvant chemotherapy is an accepted and recommended strategy providing an approximately 5% overall survival benefit at 5 years [18]. Despite this benefit and guideline recommendation, there is a slow adoption of this approach and currently only 20–50% of all patients undergoing radical cystectomy receive this form of treatment. There are no specific recommendations/guidelines on the use of neoadjuvant chemotherapy in the elderly, yet there is consensus that if an elderly individual qualifies for chemotherapy that this option should be proposed to the individual [19].

Conclusions

From nationwide registries it becomes clear that the treatment approach for young and elderly patients with nonmetastatic MIBC differs. Evaluation of a population-based cancer registry in the UK indicates that the percentage of patients who receive curative treatment drops from 52 to 12% for patients aged <60 years versus >80 years [20]. Fear of severe therapy-induced morbidity, high postoperative mortality and estimated short life expectancy are the main reasons why a less aggressive therapeutic approach is applied in the elderly. Given the lack of level I evidence any recommendation has to be based on case-series and non-randomized comparative studies. A proposed algorithm for the management of elderly patients with MIBC is presented (Fig. 1). Ideally these patients are managed by a multidisciplinary team including a geriatric assessment and in centers with experience in MIBC to avoid any delay for—potentially—curative treatment.

Conflict of interest S. Madersbacher declares that he has no competing interests.

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